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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,516	04/03/2002	Michel G. Bergeron	GGD-31611-PCTUS	5405

22202 7590 05/18/2006

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,516	BERGERON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-10,12-20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-10,12-20 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 3-10, 12-20 and 24-27 are pending.

2. In view of the amendment filed 3/6/06, the following rejections remain.

3. Claims 3-10, 12-20, 24 and 26 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any formulation which comprises antibody molecule coupled to any liposome wherein the formulation binding to HLA-DR protein present at the surface of any infectious agent and the membrane of a cell as set forth in claims 3-10, 12-20, 24 and 26.

The claims encompasses any formulation which comprises antibody or binding fragment thereof that binds to HLA-DR coupled to any liposome wherein the HLA-DR present at the surface of any infectious agent. However, the specification discloses only anti-HLA-DR immunoliposome comprising an antibody or binding fragment thereof that binds specifically to HLA-DR coupled to the specific liposomes such as the ones discloses on page 7. The only one infectious agent that expressed HLA-DR is HIV virus.

With the exception of the specific formulation comprising the specific anti-HLA-DR being coupled to the specific liposome wherein the anti-HLA antibody is capable of binding to HLA protein present at the surface of HIV or at the membrane surface of host cells such as CD4+ T lymphocytes, monocytes and macrophages, there is insufficient written description about the HLA-DR protein present at the surface of any other infectious agent other than HIV. The only infectious agent that expressed HLA-DR is HIV virus. The rest of the infectious agents that expressed the HLA-DR protein are not adequate described.

Further, the specification discloses liposome such as the ones recited in claims 3-9, the formulation comprising an antibody molecule coupled to the specific liposome and wherein the antibody or antigen binding fragment thereof binds to HLA-DR protein present at the surface of HIV, the formulation comprising said antibody molecule coupled to any liposome other than the ones recited in claims 3-9 is not adequately described.

The specification discloses only anti-HLA-DR antibody being coupled to the specific liposome as set forth on page 7, lines 5-25 wherein the HLA-DR protein present at the surface of only HIV as the infectious agent, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of liposomes and infectious agent that has HLA-DR protein present at its surface to describe the genus for the claimed formulation. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 2 have been canceled and the dependency of the claims has been changed to be now dependent on claim 24.

In response, claims 24 and newly submitted claim 26 still recite a formulation comprising an antibody molecule that binds to HLA-DR coupled to any liposome wherein the HLA-DR protein present at the surface of any infectious agent.

The specification discloses only anti-HLA-DR immunoliposome comprising an antibody or binding fragment thereof that binds specifically to HLA-DR coupled to the specific liposomes such as the ones discloses on page 7. The one and only infectious agent that expressed HLA-DR is HIV virus. Accordingly, the other liposome and infectious agent in the claimed formulation are not adequately described.

The specification discloses only anti-HLA-DR antibody being coupled to the specific liposome as set forth on page 7, lines 5-25 wherein the HLA-DR protein present at the surface of only HIV as the infectious agent, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of liposomes and infectious agent that has HLA-DR protein present at its surface to describe the genus for the claimed formulation. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 10, 12-20 and 24-27 stand rejected under 35 U.S.C. 102(b) as being anticipated by EP 0286418 A1 (December 10, 1988; PTO 1449) as evidence by Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 1449).

The '418 patent teaches a formulation which comprises antibodies or antibody fragments capable of binding to class II antigens (which is another name for HLA-DR) present at the surface of an infectious agent such as HIV virus and the membrane of a host cell such as monocytes or CD4 positive lymphocytes wherein the reference antibody being coupled to a lipid comprising vesicle such as liposome (see page 15, lines 35-38, page 15, lines 20-30, in particular). The reference class II antigens inherently are HLA-DR protein as evidence by the Saaroloos et al (see page 1640, col. 1, second paragraph, in particular). The reference formulation further comprises an additional ligand that binds to CD4 (see page 15, lines 37, in particular). The reference formulation further comprises a drug such as ddCTP, azidothymidine triphosphate (AZT), (see page 15, line 35, claims 3-8, in particular). Because the reference antibody binds to HLA-DR class II protein, the reference formulation inherently binds to HLA on cell such as CD4 lymphocytes and HLA on HIV virus. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 2 have been canceled and the dependency of the claims has been changed to be now dependent on claim 24. The EP0286418A1 does not teach or suggest a formulation comprising an antibody molecule coupled to a liposome, wherein the formulation binds to HLA-DR protein present at the surface of an infectious agent and the membrane surface of a cell as claimed in amended claim 24. In fact, liposomal formulations comprising "antibody or antibody fragments (directed) either against CD4 or against coat polyprotein of the (HIV) virus".

In contrast to applicants' assertion that the EP0286418A1 does not teach or suggest a formulation comprising an antibody molecule coupled to a liposome, wherein the formulation

binds to HLA-DR protein, the EP 0286418 A1 teaches a formulation which comprises antibodies or antibody fragments capable of binding to class II antigens (which is another name for HLA-DR) present at the surface of an infectious agent such as HIV virus and the membrane of a host cell such as monocytes or CD4 positive lymphocytes wherein the reference antibody being coupled to a lipid comprising vesicle such as liposome (see page 15, lines 35-38, page 15, lines 20-30, in particular). The reference class II antigens inherently are HLA-DR protein as evidence by the Saaroloos et al (see page 1640, col. 1, second paragraph, in particular). Because the claimed formulation is the same as that taught by the EP028641A1, the reference formulation inherently binds to HLA-DR class II protein on T cell such as CD4 lymphocytes and/or HLA-DR class II protein present on HIV virus. Further, a product is a product, irrespective of its intended use.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 10, 12-18 and 24-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (of record, Antiviral Research 33: 11-20, 1996; PTO 892) or Desormeaux et al (J Drug Targeting 6(1): 1-15, 1998; PTO 1449) each in view of Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 1449) and Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892).

Selvam et al teach a formulation which comprises an antibody such as anti-CD4 (whole) capable of binding to CD4 expressed on infectious agent such as HIV virus and CD4+ T cells wherein the reference antibody is coupled to a lipid-comprising vesicle such as liposome (See abstract, page 15, col. 1, in particular). The reference formulation comprises a drug such as 20-mer antisense DNA sequence of the rev HIV-1 regulatory gene in the form of phosphorothioate oligonucleotide against infectious agent such as HIV (see abstract, in particular). Selvam et al teach tagging liposome with anti-CD4 monoclonal antibody would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

Desormeaux et al teach a formulation which comprises a ligand such as antibodies capable of binding to CD4 expressed on infectious agent such as HIV virus and CD4+ T cells wherein the reference ligand is coupled to a lipid-comprising vesicle such as liposome (See entire document, abstract, page 3, col. 1, in particular). The reference formulation further comprises an anti-viral drug such as ZAT, ddC, foscanet, ddITP, (see page 3, col. 1, Drug containing liposmes against HIV infection, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

The claimed invention in claim 24 differs from the teachings of the references only in that the formulation wherein the antibody is capable of binding to a HLA-DR protein.

The claimed invention in claim 17 differs from the teachings of the references only in that the formulation wherein the antibody is capable of binding to a HLA-DR protein and further comprises an additional ligand to CD4.

Saarloos et al et al teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular).

Catin et al teach infectious agent such as HIV acquired host protein such as HLA-DR, ICAM-1 (CD54), CD55 (DAF), CD59, CD63 and CD71 (see page 1922, col. 1, in particular). Catin et al teach antibody to HLA-DR or anti-LFA-1 (CD11a) inhibit HIV infection since HIV virus acquired host cellular protein on the surface of the progeny virus (see page 1922, col. 1, in particular). Catin et al teach CD4 molecule is the primary cell surface receptor for HIV-1 (page

1922, col. 2, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 (see page 1922, col. 2, in particular). The reference HLA-DR protein is expressed in lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages (see page 1922, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to either substitute the anti-CD4 antibody or combine the anti-CD4 antibody capable of binding to CD4 protein in the anti-CD4 ligand that coupled to liposome as taught by Selvam et al or Desormeaux et al for the anti-HLA-DR ligand that binds to the surface of HIV and at the membrane surface of T cells as taught by Saarloos et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular). Saarloos et al et al teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Applicants' arguments filed 3/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 2 have been canceled and the dependency of the claims has been changed to be now dependent on claim 24. There is no teaching or suggestion in Selvam et al. of an antibody molecule binding to a protein present at the surface of an infectious agent, and even less of a formulation that binds to a HLA-DR present at the surface of an infectious agent. Therefore, the Applicant respectfully submits that Selvnm et al. does not teach or suggest a formulation which binds to both HLA-DR protein present at the surface of an

infectious agent and at the membrane surface of a cell as claimed in independent claims 24 and dependent claims therefrom. Additionally, Saarloos et al. teach "anti-HLA-DR that binds to HLA-DR protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage". To the contrary of the Examiner's assertions, the Applicant was not able to locate any passage in Saarloos et a1 which discussed an antibody binding to HLA-DR present at the membrane surface of a cell such as CD4+ T cells and macrophage. In addition, there is no motivation to combine the cited references as none of them teach or suggest formulation (comprising a liposome coupled to an antibody molecule), which binds to a protein present at the surface of an infectious agent.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. This rejection would have rejected under 35 USC 102(b) had Selvam et al taught a formulation which comprises an antibody such as anti-HLA-DR (whole) coupled to a lipid-comprising vesicle such as liposome.

In response to applicants' argument that Saarloos et a1 does not teach antibody binding to HLA-DR present at the membrane surface of a cell such as CD4+ T cells and macrophage, applicants' attention is directed to page 1642, col. 1, in particular.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teachings of the Selvam et al and Desormeaux et al pertaining to the used of anti-CD4 coupled to liposome to target the liposome containing drug to CD4 expressed on T cells and/or HIV virus, the teachings Saarloos et al pertaining to anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage, and the teachings of Catin et al pertaining to CD4 and HLA-DR protein is one of the

most abundant host derived protein acquired by HIV-1 and HIV-2 from host CD4 and HLA-DR protein on lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages would have led to one of ordinary skill in the art at the time the invention was made with the expectation of success to substitute the anti-CD4 coupled to liposome as taught by the Selvam et al or Desormeaux et al for the anti-HLA-DR class II protein as taught by Saarloos et al or combining the two antibodies coupled to liposome to target the formulation containing drug to HIV infectious agent and HIV trophic cells such as lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages as taught by Catin et al.

9. Claims 3-9 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (of record, Antiviral Research 33: 11-20, 1996; PTO 892) or Desormeaux et al (J Drug Targeting 6(1): 1-15, 1998; PTO 1449) each in view of Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 1449) and Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 10, 12-18 and 24-27 and further in view of US Pat No 5,773,027 (of record, June 30, 1998; PTO 892).

The combined teachings of Selvam et al, Desormeaux et al, Saarloos et al and Catin et al have been discussed supra.

The invention in claim 3 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1:1 wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

The invention in claim 4 differs from the teachings of the references only in that the formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.

The invention in claim 5 differs from the teachings of the references only in that the formulation wherein the liposome wherein the polyethyleneglycol has a molecular weight between 500 and 5000 daltons.

The invention in claim 6 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3.

The invention in claim 7 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine:

diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3.

The invention in claim 8 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or disterearolyphosphatidylcholine: distearoylphosphatidycholine: distearoylphosphatidylglycerol in a molar ratio of 10:3.

The invention in claim 9 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoyphophatidylethanolmine-polyethyleneglycerol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitolyphosphatidycholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83.

The invention in claim 19 differs from the teachings of the references only in that the formulation which comprises a drug wherein the drug is selected from the group consisting of AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palimitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, liens 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in

particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to anti-HLA-DR capable of binding to a HLA-DR protein as taught by Selvam et al, Desormeaux et al, Saarloos et al and Catin et al for the specific liposome and/or containing drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting said liposome containing drug to infectious agent such as HIV or cells such as CD4+ T cells or macrophage expressing HLA-DR as taught by the '027 patent, Selvam et al, Desormeaux et Saarloos et al and Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient drug encapsulation and drug retention and sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al

teach tagging liposome with antibody to host-derived molecules such as CD4 acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular). Saarloos et al et al teach HLA protein present at the surface of an infectious agent such as HIV is acquired from host and at the membrane surface of a cell such as CD4+ T cells and macrophage and can be detected by anti-HLA-DR antibody (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Applicants' arguments filed 3/6/06 have been fully considered but are not found persuasive.

Applicants' position is that the teachings of Selvam et al., Desormeaux et al., Saarloos et al., and Cantin et al., have been discussed above, the Applicant respectfully submits that the teachings of the '027 patent do not cure the deficiencies of the cited references. The added disclosure of the '027 patent with the above mentioned cited references does not teach nor suggest a formulation which binds to both HLA-DR protein present at the surface of an infectious agent and at the membrane surface of a cell – and even less such a formulation having the composition as claimed in claims 3-9, or further comprising a drug as claimed in claim 19.

In response, the teachings of the of Selvam et al., Desormeaux et al., Saarloos et al., and Cantin et al., have been discussed above and are incorporated here by reference. The combined teachings of the Selvam et al., Desormeaux et al., Saarloos et al., and Cantin et al. resulted in the claimed formulation comprising anti-HLA-DR antibody coupled to liposome. Since the claimed formulation is the same as that of the prior art, the inherent functions of the antibody anti-HLA-DR that coupled to liposome in the reference formulation obviously binds to HLA-DR present at the surface of HIV and/or the membrane surface on lymphocytes as taught by Saarloos et al., and Cantin et al. The '027 patent is cited for the teachings of the specific composition of the liposome recited in claims 3-9 comprising the drug such as the ones recited in claim 19 for targeting the liposome containing drug to the HIV virus as taught by the '027 patent. The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the

pharmacokinetics of drugs (See abstract, in particular). The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

10. Claim 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (of record, Antiviral Research 33: 11-20, 1996; PTO 1449) or Desormeaux et al (J Drug Targeting 6(1): 1-15, 1998; PTO 1449) each in view of Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 892) and Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 10, 12-18 and 24-27 and further in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

The combined teachings of Selvam et al, Desormeaux et al, Saarloos et al and Catin et al or have been discussed supra.

Claim 20 differs from the teachings of the references only in that the antibody molecule is anti-Fab' antibody fragment directed against a HLA-DR protein.

Harlow *et al* teach a method of producing antibody fragment such as Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment as taught by Harlow et al using the whole anti-HLA-DR as taught by Saarloos et al and then coupled to the liposome formulation as taught by Desormeaux et al, Selvam et al and Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular). One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein

acquired by HIV-1 and HIV-2 that enhances the kinetics of virus infection as taught by Catin (see page 1922, col. 2, abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular). Saarloos et al et al teach anti-HLA-DR antibody that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Applicants' arguments filed 3/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claim 11 has been canceled. The teachings of Selvam et al, Desormeaux et al., Saamloos et al., and Cantin et al., have been discussed above. The Applicant respectfully submits that the teachings of Harlow et al. do not cure the deficiency of the cited references. The added disclosure of Harlow et al. with the above mentioned cited references does not teach nor suggest a formulation which binds to both HLA-DR protein present at the surface of an infectious agent and at the membrane surface and even less a formulation wherein the antibody molecule is an anti-Fab' antibody fragment as claimed in claim 20.

In response, the teachings of Selvam et al, Desormeaux et al., Saamloos et al., and Cantin et al., have been discussed above and are incorporated here by reference.

The combined teachings of Selvam et al, Desormeaux et al, Saarloos et al and Catin et al or have been discussed supra.

Claim 20 differs from the teachings of the references only in that the antibody molecule is anti-Fab' antibody fragment directed against a HLA-DR protein.

Harlow *et al* teach a method of producing antibody fragment such as Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment as taught by Harlow et al using the whole anti-

HLA-DR as taught by Saarloos et al and then coupled to the liposome formulation as taught by Desormeaux et al, Selvam et al and Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular). One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 that enhances the kinetics of virus infection as taught by Catin (see page 1922, col. 2, abstract, in particular).

11. Claims 3-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0286418 A1 (December 10, 1988; PTO 1449) as evidence by Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 892) in view of US Pat No 5,773,027 (of record, June 30, 1998; PTO 892).

The teachings of the EP 0286418 A1 patent as evidence by Saarloos et al have been discussed supra. The EP 0286418 A1 patent further teaches antibodies and binding fragment thereof conjugated to liposome that are effective in selectively targeting liposomes containing drug to the cell type such as lymphocytes and virus without apparent side effects or toxicity (see page 15, lines 20-20-21, in particular).

The invention in claim 3 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1:1 wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

The invention in claim 4 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.

The invention in claim 5 differs from the teachings of the reference only in that the formulation wherein the liposome wherein the polyethyleneglycol has a molecular weight between 500 and 5000 daltons.

The invention in claim 6 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3.

The invention in claim 7 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3.

The invention in claim 8 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or disterearolyphosphatidylcholine: distearoylphosphatidycholine: distearoylphosphatidylglycerol in a molar ratio of 10:3.

The invention in claim 9 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoyphophatidylethanolmine-polyethyleneglycerol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitolyphosphatidycholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palimitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, liens 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The

reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to anti-HLA-DR (class II antigen) capable of binding to a HLA-DR protein as taught by EP 0286418 A1 as evidence by Saarloos et al for the specific liposome as taught by the '027 patent and further encapsulated drug such as ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting said drug to HIV as taught by the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient in drug encapsulation and drug retention; sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). The EP 0286418 A1 patent teaches antibodies and binding fragment thereof conjugated to liposome is effective in selectively targeting liposomes containing

drug to the cell type such as lymphocytes and HIV virus without apparent side effects or toxicity (see page 15, lines 20-20-21, in particular).

Applicants' arguments filed 3/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 2 have been canceled. The teachings of EP 0286418 A1 and Saarloos et al. have been discussed above. The Applicant respectfully submits that the teachings of the '027 patent do not cure the deficiencies of the cited references. The added disclosure of the'027 patent with the above mentioned cited references does not teach nor suggest a formulation which binds to both HLA-DR protein present at the surface of an infectious agent and at the membrane surface of a cell and even less such formulation having the composition defined in claims 3-9. Therefore, using the teachings of the cited references, one of ordinary skill in the art would not have been led to the claimed invention.

In response, the rejection of claims 1 and 2 is moot in view of the cancellation of said claims. The teachings of EP 0286418 A1 and Saarloos et al. have been discussed above and is incorporated here by reference. The '027 patent is cited for the teachings of the specific composition of liposome such as the ones recited in claims 3-9. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to anti-HLA-DR (class II antigen) capable of binding to a HLA-DR protein as taught by EP 0286418 A1 as evidence by Saarloos et al for the specific liposome as taught by the '027 patent and further encapsulated drug such as ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting said drug to HIV as taught by the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient in drug encapsulation and drug retention; sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of

patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

12. The following new ground of rejection is necessitated by the amendment filed 3/6/06.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "delivering a drug" in claim 26 has no antecedent basis in the formulation of claim 26 because the formulation comprising an antibody or an antibody fragment that binds to a HLA-DR protein coupled to liposome. The "drug" is not recite in formulation of the claim. Further, the claim as written is ambiguous because it is not clear if the antibody is the drug in the formulation or the drug is in the liposome. One of ordinary skill in the art cannot appraise the metes and bound of the claimed formulation.

The "antibody fragment" in claims 24 and 26 is ambiguous and indefinite because it is not clear which fragments, i.e., Fc, or binding fragment such as Fab or Fab'2 is part of the claimed invention. This rejection would be overcome by amending the claims to recite "an antigen binding fragment thereof".

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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